REMARKS

Initially, it is again noted that the Examiner failed to completely examine Applicants' invention. Specifically, Applicants object to the Examiner's failure to obtain and fully consider the references cited in the parent application and listed on the Form 1449. According to M.P.E.P. § 609:

> ...the examiner ***will consider*** information which has been considered by the Office in a parent application when examining (A) a continuation application filed under 37 CFR 1.53(b) or filed under former 37 CFR 1.60, (B) a divisional application filed under 37 CFR 1.53(b) or filed under former 37 CFR 1.60, or (C) a continuation-in-part application (see MPEP Section 201.06(b)) filed under 37 CFR 1.53(b), and a list of the information need not be submitted in the continuation, divisional, or continuation-in-part application unless applicant desires the information to be printed on the patent. (Emphasis added)

As can be seen from the above, it is mandatory for the Examiner to consider information previously considered in a parent application. The Patent Office has facilities for obtaining copies of the cited information and it is urged that the Examiner make use of these facilities. It is not reasonable, or required by Patent Office policy, for Applicants to provide additional copies of documents already considered in a parent application, especially in view of the vast number of pending applications that Applicants' Assignee, *Incyte Genomics, Inc.*, has at the Patent Office. Refusal by the Examiner to obtain and consider the documents cited in the parent application clearly is not consistent with Patent Office procedures.

Applicants Invention

The invention is based, *inter alia*, on the discovery of new human apoptosis associated proteins (HAPOP), the polynucleotides encoding HAPOP, and variants thereof, and the use of these compositions for the diagnosis of inherited and acquired genetic disorders, expression profiling, toxicology testing, and drug development with respect to diseases and disorders associated with apoptosis.

Nucleic acids encoding HAPOP-1 (SEQ ID NO:1), HAPOP-2 (SEQ ID NO:3), HAPOP-3 (SEQ ID NO:5), and HAPOP-4 (SEQ ID NO:7) of the invention were first identified in Incyte Clones 157658 from the promonocyte cDNA library (THP1PLB02), 642272 from the breast cDNA library (BRSTNOT03), 1453807 from the penis tumor cDNA library (PENITUT01), and 2059022 from the ovarian cDNA library (OVARNOT03), respectively, using a computer search

for amino acid sequence alignments. Consensus sequences, SEQ ID NO:2, SEQ ID NO:4, SEQ ID NO:6, and SEQ ID NO:8, respectively, were derived from overlapping and/or extended nucleic acid sequences.

HAPOP-1 is 480 amino acids in length and has one potential N-glycosylation site at N262; eight potential casein kinase II phosphorylation sites at S51, S130, S193, S227, S238, S371, S411, and S458; and five potential protein kinase C phosphorylation sites at S181, S193, S428, S458, and T470. Both BLOCKS and PRINTS analyses indicate that regions of HAPOP-1 show similarity to conserved motifs in ICE. These regions extend from P250 to R303, from F308 to G316, and from S344 to S363. A region of unique sequence in HAPOP-1 from about amino acid 203 to about amino acid 212 is encoded by a fragment of SEQ ID NO:2 from about nucleotide 1218 to about nucleotide 1247. Northern analysis shows the expression of this sequence in various libraries, at least 61% of which are associated with proliferating or cancerous tissue and at least 35% of which are associated with the immune response. In particular, 26% of the libraries expressing HAPOP-1 are derived from reproductive tissue.

HAPOP-2 is 238 amino acids in length and has four potential casein kinase II phosphorylation sites at S48, S62, T90, and T164 and four potential protein kinase C phosphorylation sites at S21, S36, S53, and S131. As shown in Figures 1A and 1B, HAPOP-2 has chemical and structural similarity with mouse FSP-27 (SWISS-PROT P56198; SEQ ID NO:9) and human DFF-45 (GI 2065561; SEQ ID NO:10). In particular, HAPOP-2 and FSP-27 share 79% identity, and HAPOP-2 and DFF-45 share 18% identity. In addition, the potential phosphorylation sites at S48, S62, T164, and S131 in HAPOP-2 are conserved in FSP-27, and the potential phosphorylation site at T90 in HAPOP-2 is conserved in both FSP-27 and DFF-45. Like FSP-27, HAPOP-2 is a basic protein with a predicted isoelectric point of 8.8. A region of unique sequence in HAPOP-2 from about amino acid 31 to about amino acid 40 is encoded by a fragment of SEQ ID NO:4 from about nucleotide 229 to about nucleotide 258. Northern analysis shows the expression of this sequence in various libraries, at least 55% of which are associated with proliferating or cancerous tissue and at least 48% of which are associated with the immune response. In particular, 35% of the libraries expressing HAPOP-2 are derived from reproductive tissue, and 30% are derived from gastrointestinal tissue.

HAPOP-3 is 410 amino acids in length and has one potential N-glycosylation site at N237; one potential cAMP- and cGMP-dependent protein kinase phosphorylation site at S182;

eight potential casein kinase II phosphorylation sites at S28, S182, S209, S239, S243, S247, S314, and S323; eight potential protein kinase C phosphorylation sites at S14, S28, T100, T157, T264, S301, S382, and T396; and two potential tyrosine kinase phosphorylation sites at Y137 and Y188. As shown in Figures 2A and 2B, HAPOP-3 has chemical and structural similarity with mouse Req (GI 606661; SEQ ID NO:11). HAPOP-3 and Req share 20% identity. In particular, the region of HAPOP-3 from I291 to Q391 is 44% identical to the corresponding region of Req, which comprises the cluster of four unique zinc finger motifs. All 16 cysteine and histidine residues required for metal binding in Req are conserved in HAPOP-3. A region of unique sequence in HAPOP-3 from about amino acid 36 to about amino acid 45 is encoded by a fragment of SEQ ID NO:6 from about nucleotide 181 to about nucleotide 210. Northern analysis shows the expression of this sequence in various libraries, at least 67% are associated with proliferating or cancerous tissue and at least 33% are associated with the immune response. In particular, 35% of the libraries expressing HAPOP-3 are derived from reproductive tissue, and 27% are derived from gastrointestinal tissue.

HAPOP-4 (SEQ ID NO:12) is 211 amino acids in length and has two potential N-glycosylation sites at N189 and N205; one potential casein kinase II phosphorylation site at S206; two potential protein kinase C phosphorylation sites at S63 and S206; and a potential signal peptide sequence from M1 to about C24. As shown in Figure 3, HAPOP-4 has chemical and structural similarity with hRVP1 (GI 2570129; SEQ ID NO:12). In particular, HAPOP-4 and hRVP1 share 44% identity. Hydrophobicity plots demonstrate that the four transmembrane domains of hRVP1 are well conserved in HAPOP-4 from about amino acid 1 to about amino acid 29; from about amino acid 78 to about amino acid 103; from about amino acid 120 to about amino acid 140; and from amino acid 162 to about amino acid 186. A region of unique sequence in HAPOP-4 from about amino acid 30 to about amino acid 39 is encoded by a fragment of SEQ ID NO:8 from about nucleotide 520 to about nucleotide 549. Northern analysis shows the expression of this sequence in various libraries, at least 70% are associated with proliferating or cancerous tissue and at least 30% are associated with the immune response. In particular, 38% of the libraries expressing HAPOP-4 are derived from reproductive tissue, and 24% are derived from gastrointestinal tissue.

The invention also encompasses HAPOP variants. The claimed HAPOP variants have at least 90% amino acid sequence identity to the HAPOP amino acid sequence.

The invention also encompasses polynucleotides which encode HAPOP (i.e., SEQ ID NO:2, SEQ ID NO:4, SEQ ID NO:6, and SEQ ID NO:8) and variant polynucleotide sequences encoding HAPOP. In particular, such a variant polynucleotide sequence have at least 90% polynucleotide sequence identity to the polynucleotide sequence encoding HAPOP. The polypeptides and polynucleotides of the instant invention are described through the specification.

Written description rejection under 35 U.S.C. § 112, first paragraph

The written description rejection of claims 21-22 and 27-28 under the first paragraph of 35 U.S.C. § 112 has been maintained. The rejection is traversed .

The Examiner has referred to the previous Office Action of 20 June 2000, as providing the "reasons" supporting the rejection. However, several issues set forth in that previous Office Action do not seem germane in view of the claims as amended in the paper filed 20 September 2000. In particular, the rejections set forth on pages 6 and 7 of the 20 June 2000 Office Action regarding the recitation of a "pharmaceutical composition" and "an effective amount" are not relevant, since those recitations no longer appear in the claims.

Apparently, the remaining written description issues concern the recitation of "variants" and "fragments" of SEQ ID NO:3 and SEQ ID NO:5. This rejection is respectfully traversed.

The requirements necessary to fulfill the written description requirement of 35 U.S.C. 112, first paragraph, are well established by case law.

> . . . the applicant must also convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the "written description" inquiry, *whatever is now claimed. Vas-Cath, Inc. v. Mahurkar*, 19 USPQ2d 1111, 1117 (Fed. Cir. 1991)

Attention is also drawn to the Patent and Trademark Office's own "Guidelines for Examination of Patent Applications Under the 35 U.S.C. Sec. 112, para. 1", published January 5, 2001, which provide that :

> An applicant may also show that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics[42] which provide evidence that applicant was in possession of the claimed invention,[43] i.e., complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics.[44] What is conventional or well known to one of ordinary skill in the art need not be

> disclosed in detail.[45] If a skilled artisan would have understood the inventor to be in possession of the claimed invention at the time of filing, even if every nuance of the claims is not explicitly described in the specification, then the adequate written description requirement is met.[46]

Thus, the written description standard is fulfilled by both what is specifically disclosed and what is conventional or well known to one skilled in the art.

The identification of naturally-occurring polypeptide variants with at least 90% amino acid sequence identity to SEQ ID NO:3 and SEQ ID NO: 5 would be routine for one skilled in the art based on the disclosure of the polypeptides of SEQ ID NO:3 and SEQ ID NO:5 and the polynucleotides of SEQ ID NO:4 and SEQ ID NO:6 in the instant application. While identifying a polynucleotide sequence, and the polypeptide encoded by the polynucleotide sequence, was a major undertaking at one time (even given partial nucleotide sequence data), modern methods of high-throughput nucleic acid sequencing and sequence assembly have greatly simplified the process. In fact, at the time the instant application was filed, an entire industry had already developed around the identification and testing of variant polynucleotides and polypeptides. There are countless examples of how polynucleotides and/or polypeptides of a genus have been isolated based on known properties of a species. The necessity of withholding proprietary polynucleotide and polypeptide sequence and functional data prior to obtaining some degree of patent protection is evidence of the ease and speed with which one skilled in the art can identify additional member of a genus of polynucleotide and polypeptide sequences (e.g., from genomic and cDNA libraries) given the disclosure of a species identified through diligent research efforts.

The disclosure of the instant application contains, *inter alia*, the essential elements that would allow one skilled in the art to identify expressed variant polynucleotides and polypeptides from cDNA libraries: (i) polynucleotide and polypeptide sequence data to facilitate the design of oligonucleotide primers for the identification of variants (e.g., polynucleotides that encode polypeptides with 90% sequence identity to SEQ ID NO:3 or SEQ ID NO:5), (ii) knowledge of the tissue-specific expression pattern of the polynucleotides and polypeptides to allow the selection of an appropriate cDNA library from which to identify these variants (e.g., the expression patterns described in page 19-20 of the specification of the above identified application), and (iii) an assay for the identification of variants and fragments of SEQ ID NO:3 or SEQ ID NO:5 with the disclosed biological properties (described on pages 57-58 of the

specification). Thus, given the disclosure of the instant application, it would be routine for one skilled in the art to identify naturally-variants with 90% sequence identity to the polypeptide of SEQ ID NO:3 or SEQ ID NO:5.

Similarly, given the disclosure of the full length polypeptides of SEQ ID NO: 3 and SEQ ID NO:5, the full length cDNAs of SEQ ID NO:4 and SEQ ID NO:6, and the biological assay on pages 57-58 of the instant specification, it would be routing for one skilled in the art to make and test fragments of the polypeptides of SEQ ID NO:3 or SEQ ID NO:5 for biological activity. All the essential elements have been provided in the specification, thereby making the identification of biologically active fragments prosaic for one of ordinary skill in the art.

Thus the disclosure of the instant application satisfies the written description requirements under 35 U.S.C. § 112, first paragraph, based on the literal disclosure in the specification and what was known in the art at the time the application was filed. For at least these reasons, Applicants request withdrawal of the rejections.

Utility Rejections under 35 U.S.C. §§ 101 and 112

The rejection of claims 21-22 and 27-28 is maintained on the basis that "There is no objective evidence of record that HAPOP-1, 2, 3, or 4 molecules can be used in the treatment of cell proliferative disorders and a host of other disorders affecting immunocompromised individual[s]. The data provided by Applicants suggest a correlation between the expression of he claimed sequences and various libraries. The mere expression in a tissue does not mean treatment." (Office Action, page 5).

Applicants direct Examiners attention to the enclosed BLAST report which demonstrates that the claimed polypeptides (HAPOP-2 and HAPOP-3) share clear similarity to proteins associated with apoptosis. In the case of HAPOP-2, all of the annotated top 10 BLAST hits are to proteins known to be cell death activators. The top BLAST hits are to human CIDE-A and CIDE-B (and murine homologs of these proteins) which are necessary and sufficient for inducing apoptosis in transfected cells [Inohara, N. et al. (1998) CIDE, a novel family of cell death activators with homology to the 45 kDa subunit of the DNA fragmentation factor. EMBO J. 17:2526-33]. Similarly, in the case of HAPOP-3, all of the annotated top 10 BLAST hits are to the apoptotic proteins Requiem and neuroD4 (ubi-d4) [Gabig, T.G. et al. (1994) J. Biol. Chem. 269:29515 and Mertsalov, I.B. et al.(2000) Mammalian Genome 11:72, enclosed]. One skilled in

the art would have no doubt that the claimed polypeptides are homologues of proteins capable of inducing apoptosis and would expect that HAPOP-2 and HAPOP-3 would also induce apoptosis. In fact, it would be unreasonable for one skilled in the art to doubt that HAPOP-2 and HAPOP-3 would cause apoptosis.

The instant Office Action refers to Bork *et al.* [(2000) Genome Res. 10:398-400] which makes certain statements that comparative sequence analysis is not 100% accurate. A margin of error accompanies any structure-function prediction based on sequence analysis but this limitation does not render such comparisons without merit. Researchers routinely perform BLAST analysis on novel polypeptide and polynucleotide sequences to predict the biological significance of these sequences. These sequence based comparisons often form the basis for further experimental design to study the structure and/or activity of the polypeptide or polynucleotide, *in vitro*, or perhaps in cell culture. These forms of analysis are further complicated by limitations of studying human molecules outside of their native context.

The question is not whether there is inherent error in the methods used to annotate the polypeptides disclosed in the instant application; the question is whether one skilled in the art would have a reasonable expectation of success in using SEQ ID NO:3 or SEQ ID NO:5 as described above. Applicants need only prove a "substantial likelihood" of utility; certainty is not required. *Brenner*, 383 U.S. at 532. Even according to Bork *et al.*, the accuracy of structure-function predictions is alleged to range from 50-98% (Table 1, p. 399). These statistics, in addition to those found in the several references cited by Applicants in the response to the previous Office Action [*e.g.*, Brenner *et al., supra*], clearly indicate that one skilled in the art would not dismiss high-quality comparative polypeptide or polynucleotide sequence without evidence to the contrary.

As documented in the previous Office Action response, knowledge of the biological activity of a polynucleotide, or the polypeptide it encodes is not even necessary for the use of the molecule for many aspects of toxicological screening, disease diagnosis, drug discovery, and induction of apoptosis. Yet the instant disclosure provides convincing evidence of the biological activity of HAPOP which is further substantiated by more recent BLAST analysis. Applicants respectfully request that the evidence provided in the previous Office Action response be given proper consideration and that any rejections maintained after considering Applicants' evidence and remarks be supported by objective evidence.

The instant Office Action asserts that "one skilled in the art clearly would not know how to use the claimed invention." [Office Action, paragraph 11]. No evidence of this allegation has been cited by the Examiner in either the previous Office Action or the present Office Action. In contrast, Applicants have provided an abundance of evidence (see pages 11-22 of the previous Office Action response) to support the use of SEQ ID NO:3 and SEQ ID NO:5 in toxicological screening, disease diagnosis, drug discovery, and induction of apoptosis [*e.g.*, Sandra Steiner and N. Leigh Anderson, Expression profiling in toxicology -- potentials and limitations, Toxicology Letters 112-13:467 (2000); John C. Rockett, et al., Differential gene expression in drug metabolism and toxicology: practicalities, problems, and potential, Xenobiotica 29(7):655, 656 (1999); Emile F. Nuwaysir, et al., Microarrays and Toxicology: The Advent of Toxicogenomics, Molecular Genesis 24:153 (1999); and John C. Rockett and David J. Dix, Application of DNA Arrays to Toxicology, Environ. Health Perspec. 107(8):681 (1999)]. Any one of these uses is a substantial utility under 35 U.S.C. § 101 and, derivatively, 35 U.S.C. § 112, first paragraph.

For at least the reasons discussed above, the rejections should be withdrawn.

Prior Art Rejections

The rejection of claims 21 and 27 under 35 U.S.C. § 102(e) as being anticipated by U.S. Patent No. 5,919,660 (Gross *et al.*) and under 35 U.S.C. § 102(b) as being anticipated by Accession # A55302 or Gabig *et al.* [(1994) J. Biol. Chem. 269:29515-29519] has been maintained (see paragraphs 16-17 and 19 of the Office Action dated 20 June 2000). In addition, a §103 rejection of claims 21-27 was applied over Accession # A55302 or Gabig *et al.*

Gabig *et al.* [Accession No.A55302 and J. Biol. Chem. 269:29515-29519 (1994)] and Gross *et al.* describe mouse and human proteins, respectively, purported to be involved in apoptosis. The Gabig and Gross proteins contain within their protein sequences the peptide Ser-Gly-His-Pro-Ser-Cys-Leu (SGHPSCL), which corresponds to the seven amino acid residues from position 319-325 of SEQ ID NO:5.

The SGHPSC peptide sequence is present in a number of human proteins, including but not limited to Requiem (GI:5454004), ART-4 (GI:12730276), neuro-d4 (GI:4758798, GI:12741824), interferon regulatory factor 7 (GI:11436862), and histone acetyltransferase (GI:11431961, GI:6912512). This peptide sequence is a component of an atypical zinc-finger motif in which the H and C residues are believed to participate in the coordination of a metal ion

[Gabig, T.G. et al. (1994) J. Biol. Chem. 269:29515, Fig. 5B and associated text and Mertsalov, I.B. et al.(2000) Mammalian Genome 11:72, Fig. 1B and associated text; enclosed]. Whether the isolated 7-amino acid residue sequence is capable of binding a metal ion, outside the context of the complete atypical zinc-finger motif, is doubtful but the assertion that this isolated sequence is capable of not only binding a metal ion but also functioning as a transcription factor that specifically promotes the transcription of genes that cause apoptosis, is not credible.

Nonetheless, in the interest of expediting prosecution, part (c) of claim 21 has been amended to recite, "...a biologically-active fragment of the amino acid sequence of SEQ ID NO:3 or SEQ ID NO:5 having apoptotic activity *and comprising at least 30 contiguous amino acid residues...*" Such polypeptides are not described by any of the applied documents. Applicants therefore request withdrawal of the rejection.

CONCLUSION

In light of the above amendments and remarks, Applicants submit that the present application is fully in condition for allowance, and request that the Examiner withdraw the outstanding rejections. Early notice to that effect is earnestly solicited.

If the Examiner contemplates other action, or if a telephone conference would expedite allowance of the claims, Applicants invite the Examiner to contact Applicants' Attorney at (650)855-0555.

Applicants believe that no fee is due with this communication. However, if the USPTO determines that a fee is due, the Commissioner is hereby authorized to charge Deposit Account No. **09-0108. This form is enclosed in duplicate.**

Respectfully submitted,

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

Claims 26 and 31-40 have been canceled without prejudice or disclaimer.

Claims 21 and 22 have been amended. Claims 43-45 have been added.

21. (Once Amended) An isolated polypeptide comprising an amino acid sequence selected from the group consisting of:

a) an amino acid sequence of SEQ ID NO:3 or SEQ ID NO:5;

b) a naturally-occurring amino acid sequence having at least 90% sequence identity to the sequence of SEQ ID NO:3 or SEQ ID NO:5;

c) a biologically-active fragment of the amino acid sequence of SEQ ID NO:3 or SEQ ID NO:5 comprising at least 30 contiguous amino acid residues and having apoptotic activity; and

d) an immunogenic fragment of the amino acid sequence of SEQ ID NO:3 or SEQ ID NO:5 comprising at least 30 contiguous amino acid residues.

22. (Once Amended) An isolated polypeptide of claim 21, having a sequence of SEQ ID NO:3 [or SEQ ID NO:5].

-- 43. (New) An isolated polypeptide of claim 21, having a sequence of SEQ ID NO:5.

44. (New) An isolated polypeptide of claim 21 comprising a naturally-occurring amino acid sequence having at least 90% sequence identity to the sequence of SEQ ID NO:3.

45. (New) An isolated polypeptide of claim 21 comprising a naturally-occurring amino acid sequence having at least 90% sequence identity to the sequence of SEQ ID NO:5. --